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# Diffuse pain, hypophosphatemia, and a subcutaneous nodule

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## CASE SUMMARY

### History

A 52-year-old man with no significant medical history presented with diffuse pain and progressive weakness that had been present for approximately 5 years, ultimately requiring the use of a cane for ambulation. He also reported a 7-inch loss in height and a change in the shape of his chest wall. Prior evaluation included radiographic imaging that revealed multiple long bone fractures and several vertebral compression fractures and a bone scan showing multiple foci suggestive of widespread malignancy. A bone marrow biopsy ruled out multiple myeloma. Laboratory evaluation showed markedly low serum phosphate, low-normal 1,25-dihydroxy vitamin D, and phosphaturia. The patient was treated with oral phosphate, vitamin D, and calcium without improvement. The patient was referred to the National Institutes of Health (NIH) Clinical Center for further evaluation and treatment.

### Physical examination

The patient ambulated slowly and reported pain while moving from wheelchair to the examination table. Physical examination was remarkable for kyphosis and barrel chest deformity. In addition, a 1.5-cm round area of hyperpigmentation overlying a hard noncompressible nodule on the left lower back was noted (Fig 1). The remainder of the skin examination was unremarkable.

*Abbreviations used:*

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|---|---|
| ADHR: | autosomal dominant hypophosphatemic rickets |
| ARHR: | autosomal recessive hypophosphatemic rickets |
| CT: | computed tomography |
| FGF: | fibroblast growth factor |
| HPC: | hemangiopericytoma |
| PET: | positron emission tomography |
| PMTMCT: | phosphaturic mesenchymal tumor, mixed connective tissue (type) |
| TIO: | tumor-induced osteomalacia |
| XLH: | X-linked hypophosphatemia |

### Relevant diagnostic studies

Informative laboratory tests at the time of evaluation at the NIH included serum phosphorus, 1.8 mg/dL (reference range, 2.5-4.8 mg/dL); 1,25 dihydroxy vitamin D, 22 pg/mL (22-67 pg/mL); alkaline phosphatase, 456 U/L (37-116 U/L); parathyroid hormone, 160 pg/mL (16-87 pg/mL); and ionized calcium, 1.30 mmol/L (1.22-1.38 mmol/L). The tubular reabsorption of phosphate was 48% (83%-95%). The intact serum fibroblast growth factor-23 (FGF-23) concentration was 95.2 pg/mL (10-50 pg/mL).

Serum levels of alanine aminotransferase, aspartate aminotransferase, urea nitrogen, creatinine, thyroid-stimulating hormone, and insulin-like growth factor were normal. Urinary creatinine and calcium were also normal.

Positron emission tomography with computed tomography (PET/CT) scan revealed foci of increased uptake in the right mandible, left femur, left calcaneus, and left lower back (Fig 2).

### Histopathologic examination

The lower back nodule was surgically excised. Histopathologic examination was remarkable for a nodular collection of spindle cells without atypia surrounding vascular spaces in the reticular dermis

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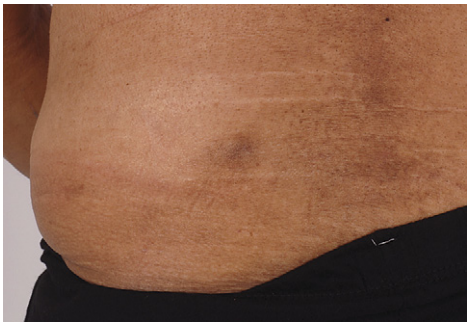

**Fig 1.** A 1.5-cm, very hard, nontender subcutaneous nodule with overlying hyperpigmentation on left lower back.

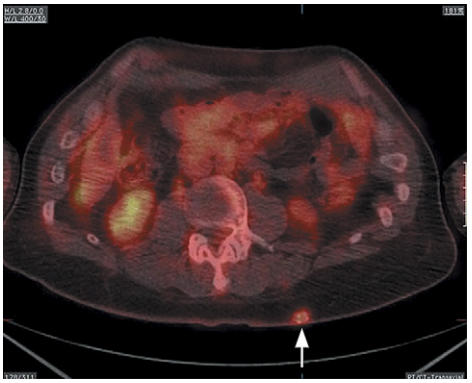

**Fig 2.** PET/CT scan: A small focus of increased uptake is observed in skin of left lower back near L3 vertebrae (*arrow*). Tumor contains areas of calcification as detected on CT component of PET/CT scan, suggestive of bone formation.

extending into the subcutis (Fig 3). The spindle cells surrounded mature lamellar bone in the dermis and did not express CD31, smooth muscle actin, or factor XIII. These findings are consistent with phosphaturic mesenchymal tumor.[1]

### Diagnosis

Tumor-induced osteomalacia (TIO) secondary to a subcutaneous phosphaturic mesenchymal tumor, mixed connective tissue type.

### Follow-up

Serum FGF-23 levels fell to below normal (5 pg/mL) immediately after surgery, and serum phosphorus and 1,25-dihydroxy vitamin D levels normalized within 7 days. The patient's muscle strength improved and pain symptoms were alleviated progressively over the ensuing 6 months. He now ambulates without assistance and has returned to work.

## DISCUSSION

Osteomalacia, or "soft bones," is a term used to describe improperly mineralized osteoid, the

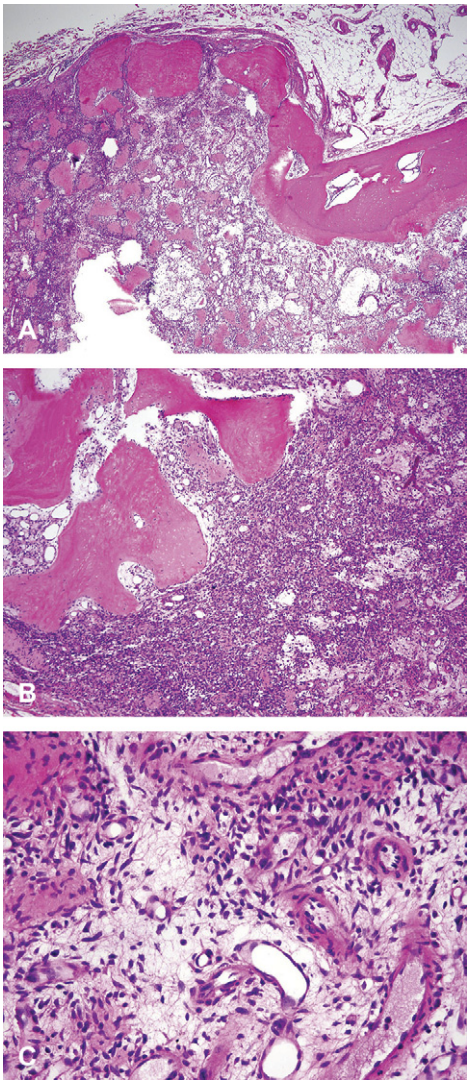


**Fig 3. A,** Phosphaturic mesenchymal tumor. Nodule consists of spindle cells, vascular spaces, and bone formation. **B**, Calcified area is true lamellar bone and is rimmed by spindle cells. **C**, Cells appear uniform without atypia. (**A-C**, Hematoxylin-eosin stain; original magnifications: **A**, ×4; **B**, ×10; **C**, ×40.)

bone protein matrix composed primarily of type I collagen. Accumulation of abnormal osteoid results in diffuse bone pain and bone fractures following minimal trauma. Osteomalacia may be congenital or acquired. Congenital causes include X-linked hypophosphatemia (XLH) as well as autosomal dominant and autosomal recessive hypophosphatemic rickets (ADHR and ARHR). Although the genetic diseases usually present during childhood with rickets, ADHR can occasionally present in adults. Acquired forms of osteomalacia result from inadequate substrate to mineralize osteoid, that is, calcium or phosphorus. Inadequate ingestion of vitamin D and/or calcium may lead to calcium deficiency, whereas acquired

forms of hypophosphatemia almost always reflect renal tubular losses. Acquired renal phosphate wasting may result from renal tubular damage from heavy metals or chemotherapy, fibrous dysplasia of bone, and TIO.[2] The shared pathway for most forms of renal phosphate wasting, including TIO, involves elevated serum FGF-23.

FGF-23 is a hormone that regulates serum phosphate and 1,25-dihydroxy vitamin D levels at the proximal renal tubule[3] and was discovered as a phosphaturic factor when mutations in the gene encoding FGF-23 were found to be the cause of ADHR.[4] Subsequently, elevated FGF-23 has been found in patients with TIO,[5] XLH,[5] ARHR,[6] and fibrous dysplasia of bone.[7] FGF-23 is made by osteocytes[7] and acts on renal proximal epithelial cells to prevent phosphate reabsorption and conversion of inactive 25-vitamin D to active 1,25-dihydroxy vitamin D.[8]

The tetrad of TIO is a very low serum phosphate level, increased urinary phosphate excretion, inappropriately low to low-normal 1, 25-dihydroxy vitamin D levels, and elevated serum FGF-23. Increased FGF-23 in TIO is due to autonomous secretion by tumor cells.[5] Using reverse transcriptase—polymerase chain reaction and immunohistochemistry, approximately 80% of tumors in patients with TIO express FGF-23.[9] Ultrastructural studies using immunogold labeling have localized FGF-23 to the rough endoplasmic reticulum in neoplastic cells,[10] demonstrating that FGF-23 is derived from tumors.

TIO is most commonly associated with slow-growing, benign mesenchymal tumors. Approximately 50% of TIO-associated tumors arise within bone and the other 50% within soft tissues. Regardless of origin of tumors, the lower extremities and craniofacial region are favored locations.[11] Histologic features include spindle and oval cells, prominent blood vessels, osteoclast-like giant cells, and a focally mucoid stroma. Cartilaginous and/or metaplastic bone formation is common. Weidner and Santa Cruz[1] classified this heterogeneous group of tumors into 4 types: phosphaturic mesenchymal tumor, mixed connective tissue type (PMTMCT); osteoblastoma-like tumors; ossifying fibrous-like tumors; and nonossifying fibrous-like tumors. Hemangiopericytoma (HPC) is described as one of the most frequent-appearing neoplasms associated with TIO.[9] However, the current consensus World Health Organization classification of soft tissue tumors discourages use of HPC as a primary diagnosis because HPCs are derived from fibroblasts, rather than pericytes as initially proposed.[12] Histopathologic review of 32 previously reported cases of TIO, including 3 classic HPCs and 24 with HPC-like vessels, led to reclassification of 80% of TIO-associated mesenchymal tumors as PMTMCT.[9]

The diagnosis of TIO can be challenging because laboratory findings can be subtle, and FGF-23 serum levels are not included on routine chemistries nor are they commercially available. Severe hypophosphatemia is an important clue and should prompt further evaluation of renal phosphate excretion, serum 1,25-dihydroxy vitamin D levels, and the calcium/parathyroid hormone axis. Low urinary reabsorption of phosphorus in the setting of hypophosphatemia and normal serum vitamin D levels is diagnostic. If diagnostic confirmation is needed, bone biopsy demonstrates prominent osteoid formation and unmineralized bone.

Resection of the FGF-23 secreting tumor is curative. A thorough skin examination should be conducted and special consideration paid to any nodule or mass. Since many tumors are small and asymptomatic, extensive imaging studies may be required to identify the source. Imaging studies employed (in order of utility) include octreotide scan (a radionuclide scan using a somatostatin analog), PET/CT, whole-body magnetic resonance imaging, and CT.[13] In instances in which imaging fails to identify a specific tumor site, regional venous sampling in conjunction with FGF-23 assays have been used to confirm tumor location as well as to determine postsurgical response.[14]

Patients typically experience rapid improvement in both clinical symptoms and laboratory abnormalities following tumor removal. Even if the tumor cannot be located or is unresectable, treatment with oral replacement of phosphate and vitamin D may provide significant symptomatic benefit.

## KEY TEACHING POINTS

- Progressive weakness and bone pain in a setting of low serum phosphorus, low-normal 1,25-dihydroxy vitamin D, and increased urinary phosphate should prompt an evaluation for TIO.
- Tumors autonomously secrete FGF-23, which induces wasting of urinary phosphorus, abnormal vitamin D metabolism, and the associated clinical signs of osteomalacia.
- Phosphaturic mesenchymal tumors, mixed connective tissue type, are the most common causes of TIO. Hemangiopericytoma-like features are often observed in these mesenchymal tumors.
- In some cases, causative tumors may be identified by skin examination.
- Complete removal of the tumor is curative.

*Editor's note*: Dr Collins is an endocrinologist in the National Institute of Dental and Craniofacial

Research who evaluates patients with TIO and familial tumoral calcinosis. Clinicians can refer interested patients to the NIH patient recruitment and referral office at 800-411-1222 or by e-mail at prpl@mail.cc.nih.gov.

**REFERENCES**

1. Weidner N, Santa Cruz D. Phosphaturic mesenchymal tumors. A polymorphous group causing osteomalacia or rickets. Cancer 1987;59:1442-54.
2. Collins MT, Chebli C, Jones J, Kushner H, Consugar M, Rinaldo P, et al. Renal phosphate wasting in fibrous dysplasia of bone is part of a generalized renal tubular dysfunction similar to that seen in tumor-induced osteomalacia. J Bone Miner Res 2001;16:806-13.
3. Imel EA, Econs MJ. Fibroblast growth factor 23: roles in health and disease. J Am Soc Nephrol 2005;16:2565-75.
4. Autosomal dominant hypophosphataemic rickets is associated with mutations in FGF23. Nat Genet 2000;26:345-8.
5. Jonsson KB, Zahradnik R, Larsson T, White KE, Sugimoto T, Imanishi Y, et al. Fibroblast growth factor 23 in oncogenic osteomalacia and X-linked hypophosphatemia. N Engl J Med 2003;348:1656-63.
6. Feng JQ, Ward LM, Liu S, Lu Y, Xie Y, Yuan B, et al. Loss of DMP1 causes rickets and osteomalacia and identifies a role for osteocytes in mineral metabolism. Nat Genet 2006; 38:1310-5.
7. Riminucci M, Collins MT, Fedarko NS, Cherman N, Corsi A, White KE, et al. FGF-23 in fibrous dysplasia of bone and its relationship to renal phosphate wasting. J Clin Invest 2003; 112:683-92.
8. Shimada T, Mizutani S, Muto T, Yoneya T, Hino R, Takeda S, et al. Cloning and characterization of FGF23 as a causative factor of tumor-induced osteomalacia. Proc Natl Acad Sci U S A 2001;98:6500-5.
9. Folpe AL, Fanburg-Smith JC, Billings SD, Bisceglia M, Bertoni F, Cho JY, et al. Most osteomalacia-associated mesenchymal tumors are a single histopathologic entity: an analysis of 32 cases and a comprehensive review of the literature. Am J Surg Pathol 2004;28:1-30.
10. Cheung FM, Ma L, Wu WC, Siu TH, Choi PT, Tai YP. Oncogenic osteomalacia associated with an occult phosphaturic mesenchymal tumour: clinico-radiologico-pathological correlation and ultrastructural studies. Hong Kong Med J 2006;12:319-21.
11. Sundaram M, McCarthy EF. Oncogenic osteomalacia. Skeletal Radiol 2000;29:117-24.
12. Fletcher CD. The evolving classification of soft tissue tumours: an update based on the new WHO classification. Histopathology 2006;48:3-12.
13. Jan de Beur SM. Tumor-induced osteomalacia. JAMA 2005; 294:1260-7.
14. Takeuchi Y, Suzuki H, Ogura S, Imai R, Yamazaki Y, Yamashita T, et al. Venous sampling for fibroblast growth factor-23 confirms preoperative diagnosis of tumor-induced osteomalacia. J Clin Endocrinol Metab 2004;89:3979-82.